An Enantioselective Two-Component Catalyst System: Rh−Pd-Catalyzed Allylic Alkylation of Activated Nitriles

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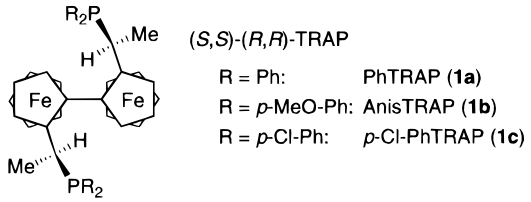
We report here a novel enantioselective reaction promoted by a two-component catalyst system consisting of two different transition metal complexes, in which the two catalysts activate their respective substrates and the resulting active species react in an enantioselective manner to produce an optically active compound.

Activated nitriles such as α-cyano esters are known to undergo aldol and Michael reactions under the influence of a catalytic amount of low-valent transition metal complexes such as $RuH_2(PPh_3)_4$ and $RhH(CO)(PPh_3)_3$,[1] and we reported the highly enantioselective Michael reaction of 2-cyanopropionates and *N*-methoxy-*N*-methyl-2-cyanopropionamide by applying our trans-chelating chiral phosphine ligand PhTRAP (**1a**)[2] in combination with $RhH(CO)(PPh_3)_3$ or $Rh(acac)(CO)_2$.[3] Mechanistic studies carried out in our laboratory[4] and others[1b,5] indicated that cyanopropionate is activated by the Rh−TRAP catalyst as delocalized ester enolate coordinating to the rhodium atom through the cyano nitrogen atom {*trans*-[Rh(N≡CCMeCO_2R)(CO)(PhTRAP)]} and that the enolate intermediate attacks an electrophile (Michael acceptor) free from coordination to the metal.



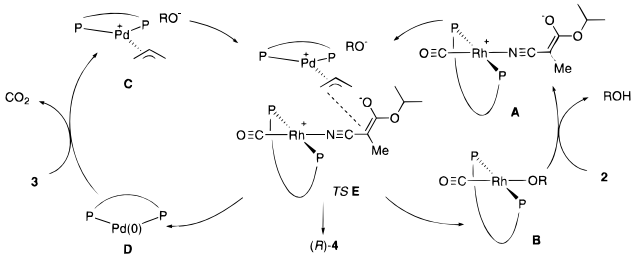
On the basis of this mechanism, we have undertaken the study of the enantioselective allylic alkylation of the activated nitriles by employing a π-allylpalladium(II) complex as an electrophile instead of the Michael acceptor. In principle, the π-allylpalladium(II) complex can be catalytically produced from an allylic carbonate and catalytic amount of palladium complex in neutral conditions (eq 1).[6] Our design of the catalytic system is shown in Scheme 1, where rhodium(I)-coordinated enolate complex **A** is initially formed from $Rh(acac)(CO)_2$, TRAP, and cyano ester **2**, while π-allylpalladium(II) complex **C** is formed by the decarboxylative oxidative addition of allyl carbonate **3** to palladium(0) complex **D**. Nucleophilic attack of the enolate (**A**) to the π-allylpalladium(II) complex (**C**) occurs enantioselectively (TS **E**) to produce optically active product **4**. At this step, the palladium(0) (**D**) is reproduced and RO^- becomes a ligand of the rhodium atom to form alkoxo rhodium(I) complex **B**. The catalytic system is completed by the proton exchange between **B** and **2**, forming the enolate complex (**A**) and ROH.

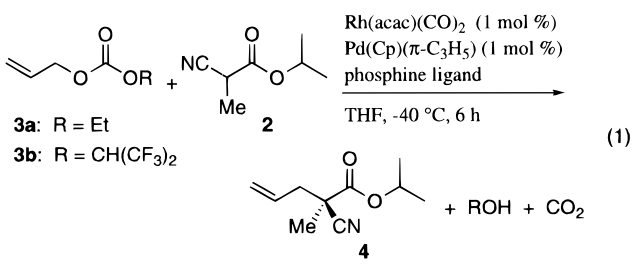
Table 1. Enantioselective Allylation of **2** with **3** Promoted by the Rh−Pd Catalytst System (eq 1)[a]

entry	**3**	Pd[b]	Rh[b]	ligand	temp (°C)	time (h)	yield[c] (%)	ee[d] (%)
1	**3a**	+	+	**1a**	0	4	98	32 (*R*)
2	**3a**	+	−	**1a**	0	5	97	0
3	**3a**	−	+	**1a**	0	24	0	
4	**3b**	+	+	**1a**	−25	5	91	93 (*R*)
5	**3b**	+	−	**1a**	−25	24	91	0
6	**3b**	+	+	**1b**	−25	4	93	97 (*R*)
7	**3b**	+	+	**1b**	−40	6	93	99 (*R*)
8	**3b**	+	+	**1c**	−25	24	84	54 (*R*)

[a] Solvent is THF. (*S*,*S*)-(*R*,*R*)-TRAP was used for all entries. **2** (0.5 M)/**3** = 1/2. [$Rh(acac)(CO)_2$ + $Pd(Cp)(\pi\text{-}C_3H_5)$]/ligand = 1/1. [b] +: **2**/cat = 100/1. −: without catalyst. [c] Isolated yield by bulb-to-bulb distillation; conversion was complete except for entry 3. [d] Determined by GLC analysis of **4** with a chiral capillary column Chiraldex G-TA.

Scheme 1





In our initial attempt, allyl ethyl carbonate **3a** was employed as an substrate for the alkylation of **2** (Table 1, entries 1−3). In the presence of 1 mol % each of $Rh(acac)(CO)_2$ and Pd(Cp)(π-C_3H_5) together with (*S*,*S*)-(*R*,*R*)-PhTRAP (**1a**) as a ligand for both the rhodium and palladium catalysts [(Rh + Pd):TRAP = 1:1],[7] the reaction proceeded smoothly in THF at 0 °C (4 h) to give **4** with a low but apparent enantiomeric excess [32% ee (*R*)] (entry 1). The sense of enantioselection is the same as that for the Michael reaction of **2** as expected from the

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(4) Reaction of $Rh(acac)(CO)_2$, TRAP, and $NCCHMeCO_2R$ (1:1:1) gave *trans*-[Rh(N≡CCMeCO_2R)(CO)(TRAP)] in a quantitative yield. The structure was assigned on the basis of NMR and IR spectra and elemental analysis: Sawamura, M.; Sudoh, M.; Hamashima, H.; Ito Y. Unpublished results.

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(7) While generally prefering trans-coordination, TRAP should be cis-coordinated in π-allylpalladium complex **C**. The cis-coordination of PhTRAP was confirmed for the related π-allylpalladium complex prepared by mixing [Pd(π-C_3H_5)(COD)]BF_4 and PhTRAP in $CDCl_3$: $^{31}P\{^1H\}$ NMR ($CDCl_3$, 85% H_3PO_4) δ 29.2 (d, J = 35.5 Hz), 33.9 (d, J = 35.5 Hz).

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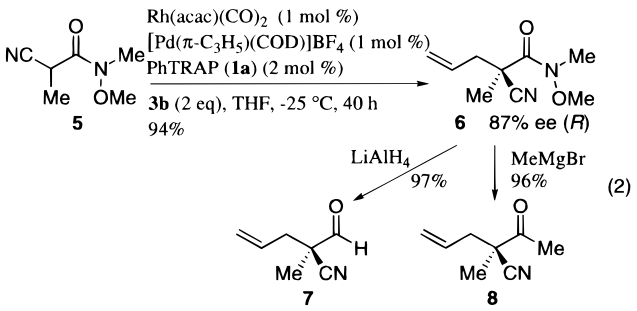
mechanism shown in Scheme 1. The control reaction (entry 2) catalyzed only by the Pd−PhTRAP catalyst proceeded in a comparable rate, but the product was racemic; however, no reaction was catalyzed by the Rh−PhTRAP catalyst in the absence of the palladium catalyst (entry 3). These results indicate that the TRAP ligand on the palladium atom has no effect in terms of enantioselectivity as expected from the established mechanism of palladium-catalyzed allylic alkylation of a stabilized carbon nucleophile, in which the nucleophile attacks a π-allyl carbon from the side opposite to the palladium atom (see TS **E**).[8] We reasoned that the low enantioselectivity in the reaction catalyzed by both the rhodium and palladium catalysts would be due to a reaction pathway in which the rhodium catalyst does not participate in the formation of the cyano ester enolate, but free ethoxide anion abstracts the α-proton of **2** and that this undesired reaction pathway would be suppressed by employing a carbonate substrate releasing RO^- with lower basisity and higher affinity to the rhodium atom.

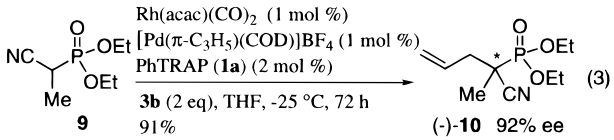
As demonstrated in entries 4 and 5 (Table 1), this was achieved with allyl hexafluoroisopropyl carbonate (**3b**), from which $(CF_3)_2CHO^-$ is formed. Its basisity is considerably decreased by the strong electron-withdrawing effect of the CF_3 group, and at the same time its soft character as an alkoxo ligand is expected to be favorable for the coordination to the soft rhodium(I) complex {*trans*-[Rh(CO)(PhTRAP)]$^+$}. Thus, the allylation of **2** with the fluorinated carbonate **3b** catalyzed by the Rh−Pd−PhTRAP system proceeded smoothly at −25 °C and was completed in 5 h to give **4** with an enantiomeric excess as high as 93% (*R*) (entry 4). On the other hand, the reaction in the absence of the rhodium catalyst proceeded more slowly to give totally racemic product (entry 5). This control experiment shows that the trapping of $(CF_3)_2CHO^-$ by *trans*-[Rh(CO)(PhTRAP)]$^+$ was efficient enough to avoid the undesired direct deprotonation.

The selectivity was increased to 97% ee by employing the electron-rich ligand (*S*,*S*)-(*R*,*R*)-AnisTRAP (**1b**) (entry 6) and reached 99% ee by carrying out the reaction at −40 °C (entry 7), while the use of the electron-deficient ligand (*S*,*S*)-(*R*,*R*)-*p*-Cl-PhTRAP (**1c**) resulted in the drastic decrease in the selectivity (54% ee, entry 8). The nucleophilicity of rhodium(I)-coordinated enolate **A** should be higher for the complex with more electron-donating ligand. Taking it into consideration that the progress of reaction was still observed in the absence of the rhodium catalyst (entry 5), the ligand electronic effects may be explained by the difference in the rate of nucleophilic attack of **A**.

This two-component catalyst system is applicable to the enantioselective allylation of *N*-methoxy-*N*-methyl-2-cyanopropionamide (**5**), Weinreb amide version of **2** (eq 2).[3c] The conversion of product **6** {$[\alpha]^{20}_D$ −21.8 (*c* 1.08, $CHCl_3$)} into the aldehyde (**7**) and ketone (**8**) demonstrates its rich synthetic utility.



The allylation of diethyl (1-cyanoethyl)phosphonate (**9**) was also proceeded with high enantioselectivity to give an interesting optically active phosphonic acid derivative {(−)-**10**, $[\alpha]^{20}_D$ −22.8 (*c* 1.03, $CHCl_3$), configuration not determined} (eq 3).



Since the TRAP ligand on the palladium atom does not play any important role in terms of enantioselectivity, we reasoned that it would be possible to use an achiral phosphine ligand for activation of the palladium catalyst. The catalyst system consisting of Rh(acac)(CO)$_2$−PhTRAP (1 mol %) and Pd(Cp)(π-C_3H_5)−dppb (1 mol %) efficiently promoted the allylation of **2** with **3b** at −40 °C to give **4** with 93% ee (see the supporting information for the experimental procedure).[9] Interestingly, the identical enantioselectivity was obserbed even when PhTRAP and dppb were replaced with each other (Rh−dppb, Pd−PhTRAP). While any definite conclusions must await more mechanistic studies by NMR, these results may possibly suggest that TRAP and dppb prefer the rhodium and palladium complexes, respectively, and the ligand exchange is fast enough to achieve an equilibrium governed by the ligands' preferences.

Supporting Information Available: Experimental procedures including determination of the absolute configuration of **4** and **6** (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS; and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(9) The use of dppb for the allylation of Weinreb amide **5** (eq 2) caused an apparant decrease in enantioselectivity (PhTRAP, −25 °C, 48 h, 92%, 77% ee).